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Rates of adverse outcomes and revision surgery following anterior cruciate ligament (ACL) reconstruction: a study of 110,945 procedures using the national hospital episodes database for England, UK

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ABSTRACT

BACKGROUND

Following ACL injury, ACL reconstruction is an elective procedure and therefore an understanding of the attributable risk from undergoing ACL reconstruction is necessary for patients to make a fully informed treatment decision.

PURPOSE

To determine the absolute risk of adverse outcomes including reoperation following ACL reconstruction with comparison, where possible, to the rate of adverse events reported in the general population.

STUDY DESIGN

Cohort study

METHODS

National hospital data on all ACL reconstructions performed in England between April 1, 1997 and March 31, 2017 were analysed. Revision cases, bilateral procedures within 6 months, and cases with concurrent cartilage or multiple ligament surgery were excluded. The primary outcome was the occurrence of at least one serious complication (myocardial infarction, stroke, pulmonary embolism, infection requiring surgery, fasciotomy, neurovascular injury, or death) within 90-days. Additionally, 5-year rates of revision ACL reconstruction, contralateral reconstruction, and meniscal surgery were investigated.

RESULTS

133,270 ACL reconstructions were performed of which 104,255 were eligible for analysis. Within 90 days, serious complications occurred in 675 (0.65%; 95% confidence interval [CI] 0.60-0.70), including 494 reoperations for infection (0.47%; 95% CI 0.43-0.52) and 129 pulmonary embolisms (0.12%; 95% CI 0.10-0.15). Of 54,275 patients with at least 5 years follow-up, 1746 (3.22%; 95% CI 3.07-3.37) underwent revision ACL reconstruction in the same knee, 1553 contralateral ACL reconstruction (2.86%; 95% CI 2.72-3.01), and 340 (0.63%; 0.56-0.70) subsequent meniscal surgery. The overall risk of serious complications fell over time (adjusted odds ratio [OR] 0.96 per year; 95% CI 0.95-0.98) however older patients (adjusted OR 1.11 per 5-years; 95% CI 1.07-1.16) and patients with a greater modified Charlson comorbidity index (adjusted OR 2.41 per 10-units; 95% CI 1.65-3.51) were are higher risk. For every 850 (95% CI 720-1039) ACL reconstructions

done, one pulmonary embolism could be provoked. For every 213 (95% CI 195-233), one native knee joint infection could be provoked.

CONCLUSION

The overall risk of adverse events following ACL reconstruction is low, however some rare but serious complications, including infection or pulmonary embolism, may occur. Around 3% of patients undergo a further same side or opposite side ACL reconstruction within five years. These data will inform shared decision making between clinicians and patients considering their treatment options.

What is known about this subject

- Before this study, several systematic reviews have attempted to estimate the risk of adverse events after ACL reconstruction however the findings have been limited by small numbers of studies, small number of patients, non-representative data sources, and concerns about incomplete data capture.
- For infection rates, a systematic review of level 2 studies published in 2017 reported a 0.43% deep infection rate (58/13401; 95% CI 0.32 to 0.56). For pulmonary embolism, a systematic review of 47 included studies published in 2016 reported a rate of 0.14% (1/704; 95% CI 0.00 to 0.79). A rate of revision ACL reconstruction of 3.59% (587/16336; 95% CI 3.31 to 3.89) was reported from a large military health database series in 2016. A systematic review published in 2015 previously estimated a 12.5% (335/2682) risk of contralateral ACL injury.

What this study adds to existing knowledge

- ACL reconstruction was associated with a 0.65% risk of serious complications within 90 days (pulmonary embolism, infection requiring surgery, myocardial infarction, stroke, fasciotomy, neurovascular injury, death).
- Using comparative general population data, it was determined that for every 850 fewer ACL reconstructions performed, one pulmonary embolism and four native knee joint infections could be provoked.
- Within 5-years, 3.2% patients require revision ACL reconstruction in the same knee, 0.63% undergo meniscal surgery in the same knee, and 2.9% undergo ACL reconstruction in the opposite knee.

Women are at lower risk of revision surgery and meniscal surgery but not opposite side reconstruction, in comparison to men.

- Although the risk of adverse events after ACL reconstruction is greater than after arthroscopic partial meniscectomy, the overall risk from this type of surgery remains low.
- Nevertheless, as ACL reconstruction may be an avoidable intervention for many people following ACL injury, this new understanding of risk and reoperation rates is crucial for patients to be able to make an informed treatment decision.

INTRODUCTION

The incidence of anterior cruciate ligament (ACL) injury in the population is approximately 0.03% per year, rising to over 3% in studies of certain professional athletes.[26] Reconstruction of the ACL is frequently recommended due to functional impairment and concerns about the development of meniscal or articular cartilage damage from recurrent instability of the knee.[15,35] The population rate of ACL reconstruction ranges from approximately 8 to 52/100,000 people between countries;[5,26] in England, the intervention rate was 24/100,000 in 2016-17.[2]

In 2010, a clinical trial indicated that for many patients with an ACL injury, a strategy of rehabilitation with optional delayed ACL reconstruction may avoid the need for surgery.[16] Other groups, however, continue to advocate early reconstruction due the risks of cartilage and meniscal damage from recurrent knee instability.[11,14,16,19,25] As ACL reconstruction is an elective procedure, besides the anticipated benefits of undergoing the procedure, it is crucially important for patients and clinicians to have knowledge of the specific risks.[6] Before this study, several studies have attempted to estimate the risk of adverse events after ACL reconstruction.[4,13,21,22,24,32–34] The findings, however, have generally been limited by small numbers of studies, small number of patients, non-representative data sources, and concerns about incomplete data capture.

The purpose of this study was to determine the risks of adverse outcomes following anterior cruciate ligament reconstruction within 90-days of surgery, with comparison, where possible, to the rate of adverse events reported in the general population. The secondary aim was to examine the risk of subsequent ipsilateral and contralateral ACL reconstruction within 5-years.

METHODS

Data source

National Hospital Episode Statistics (HES) data was obtained from NHS Digital (application DARS-NIC-68703) and linked with the Office for National Statistics (ONS) mortality dataset. HES contains a record of all patient attendances at NHS hospitals in England, covering episodes of care delivered in treatment centres (including those in the independent sectors) funded by the NHS, episodes of care in England where patients are resident outside of England, and privately funded patients treated within NHS England hospitals.[28] The information recorded in the HES database includes patient demographic and residence data, primary and secondary diagnoses including comorbidities, and all procedures undertaken. The ONS mortality dataset contains national death certificate data, irrespective of whether the death occurred in hospital or in the community.

Procedures

All HES records between 1 April 1997 and 31 March 2017 were extracted for patients undergoing ACL reconstruction. Episodes were identified from the Classification of Surgical Operations and Procedures (OPCS-4) codes in the procedure fields within the HES data (W742 [excluding repair or synthetic graft procedures W841, W842, W723, W724]).[29] Simultaneous or staged (within 6 months) bilateral cases were excluded along with cases with concurrent articular cartilage or multiple ligament surgery. Per patient, per side, only the first (primary) ACL procedure was included as an index procedure. For each patient identified as undergoing an index ACL reconstruction, all the patient's prior and subsequent hospital episodes were identified for the entire data extraction period. Subsequent revision procedures in the same patient were not eligible for analysis as index procedures but were analysed as reoperation outcomes (see Outcomes, below). Cases missing essential data (age, sex, procedure date, procedure laterality) were excluded from the study. Cases missing non-essential data (index of multiple deprivation, ethnicity, rurality) were included except for analyses adjusting for these specific variables.

Outcomes

Complications were identified by a review of a combination of the twenty International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis fields per hospital episode and twenty-four OPCS operation fields per episode.[29,39] Complications identified from the ICD-10 diagnosis fields were as follows: pulmonary embolism (PE), myocardial infarction, stroke, lower respiratory tract infection, acute kidney injury, urinary tract infection, and neurovascular injury. Complications identified from the OPCS operation codes were confirmed to match with the laterality (left versus right) of the index procedure using the OPCS laterality codes. The procedure-based complications were as follows: joint infection, fasciotomy, general reoperation (any surgical procedure performed in the same knee within 90 days), revision ACL reconstruction, meniscal surgery, contralateral ACL reconstruction. Mortality data was extracted from the ONS mortality fields. The primary outcome was the occurrence of at least one serious complication within 90-days of an index ACL reconstruction. A serious complication was defined as either myocardial infarction, stroke, pulmonary embolism, infection requiring surgery (open or arthroscopic irrigation and lavage or debridement [excluding haemarthrosis]), fasciotomy, neurovascular injury, or death. The rate of each individual complication was then evaluated secondarily, with each complication counted whether in isolation of in combination with other adverse outcomes. The secondary outcomes were revision ACL reconstruction procedures, subsequent meniscal surgery procedures in the same knee, and contralateral knee ACL reconstruction procedures within 5-years.

Statistical analysis

Stata v15.1 (StataCorp, College Station, Texas, USA) was used to perform all analysis. Descriptive statistics were used to report demographic data. Complication rates were reported with confidence intervals corresponding to the proportion of the study sample. Logistic regression methods were used to first calculate the unadjusted odds of each complication occurring within 90-days by age, sex, index of multiple deprivation (quintile derived from regional factors in England including average

income, employment, education, housing, and crime; 1=least deprived area, 5=most deprived),[30] ethnicity, modified Charlson comorbidity index (Summary Hospital-level Mortality Indicator Specification; derived with a maximum 5-year ICD-10 diagnosis code lookback period),[7,20,41] year of treatment, ethnicity, and rurality. The odds ratios were then adjusted including all these variables in the same statistical model. Cox proportional hazards modelling, adjusted in the same manner, was used to identify associations with same side revision ACL reconstruction, contralateral ACL reconstruction, and same side meniscal surgery. Long-term rates of revision ACL reconstruction were also assessed using a mortality adjusted Kaplan-Meier survival analysis (not undergoing revision surgery).

In order to guide patients and clinicians regarding the relative risk of undergoing the procedure, age-sex matched general population study data was reviewed where available in published data. Population and adverse event numbers were extracted from the ONS national mortality report and from publications reporting population rates of myocardial infarction, pulmonary embolus, stroke, and septic arthritis respectively.[10,12,17,36,38] Annualised rates were adjusted directly to estimate 90-day complication rates. The relative risk (risk ratio) of adverse events was calculated, where possible, by comparing the adverse event rate in an age-sex matched sample of patients in the general population. The number needed to harm (NNH) was calculated from the risk difference between the study cohort and the general population data (attributable risk).

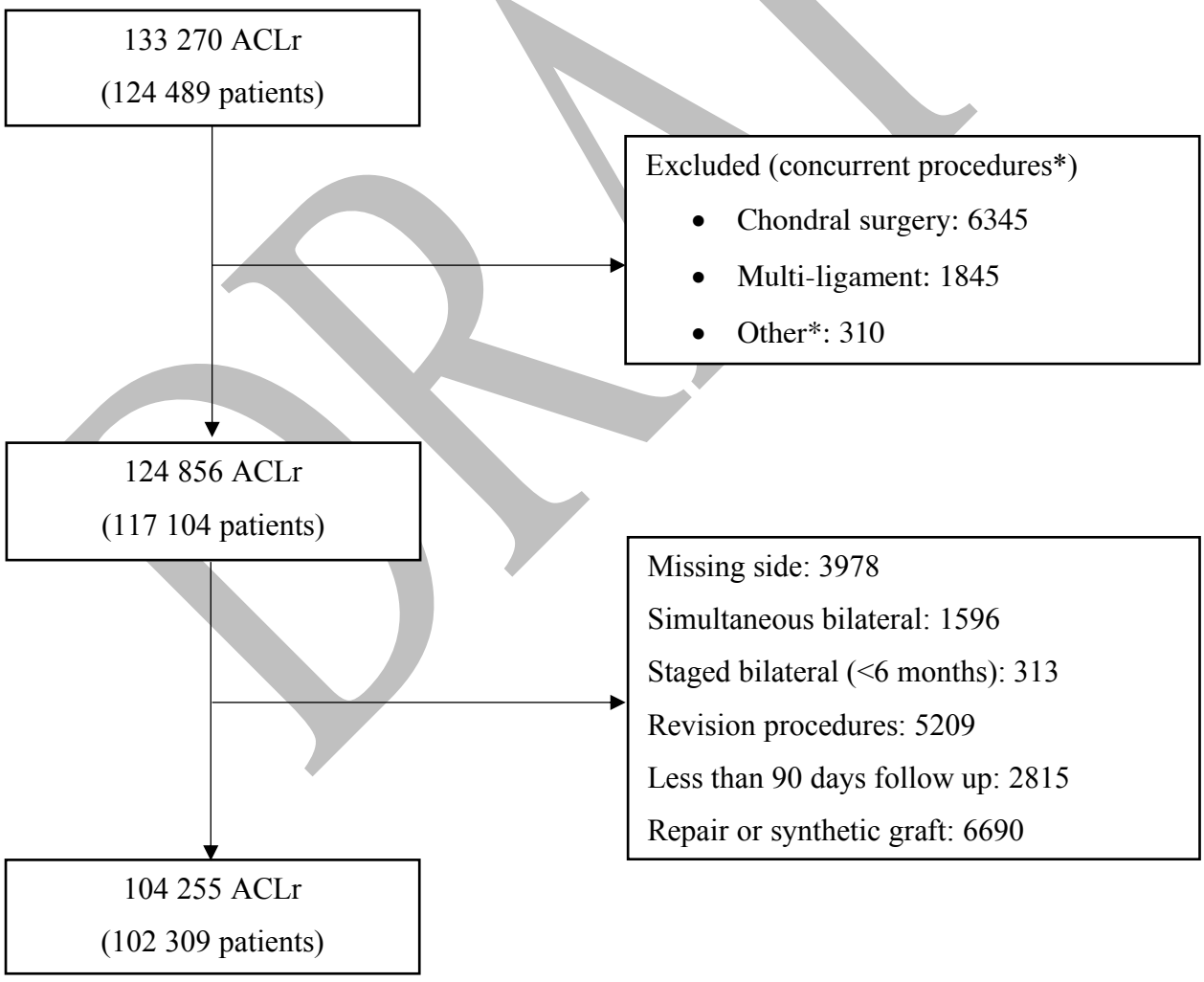
Role of the funding source

The sponsors of the study had no role in the design or conduct of the study. All authors take responsibility for the contents of the study and the decision to proceed to publication.

RESULTS

Between 1 April 1997 and 31 March 2017, 133 270 ACL reconstructions (124 489 patients) were identified of which 104 255 (102 309 patients) were included (Figure 1). The mean age of the case cohort was 29.2 years (SD 9.68) and 23 435 (22.5%) were performed in female patients (Table 1). The majority of patients had no record of comorbidities (modified Charlson index zero; 90.65%), were of white ethnicity (75.62%), and from urban regions (79.97%) (Table 1). For five-year follow-up ipsilateral ACL and meniscal surgery and contralateral ACL reconstruction, data was available for 54,275 procedures (Table 2).

Figure 1: Case selection



** Same side or contralateral surgical procedures (not mutually exclusive). Other procedures included knee arthroplasty, fusion, interposition.*

TABLE 1: Demographics

	n	%
All procedures		
Total	104 255	100%
Sex		
Male	80820	77.52% (77.27, 77.77)
Female	23435	22.48% (22.23, 22.73)
Age group (years)		
<20	15357	14.73% (14.52, 14.95)
20-39	72331	69.38% (69.10, 69.66)
40-59	16069	15.41% (15.19, 15.63)
60-79	475	0.46% (0.42, 0.50)
80+	23	0.02% (0.01, 0.03)
Charlson index		
0	94503	90.65% (90.47, 90.82)
1 - 15	9711	9.31% (9.14, 9.49)
16 - 30	39	0.04% (0.03, 0.05)
31 - 50	2	0.00% (0.00, 0.01)
IMD		
1	21761	20.87% (20.63, 21.12)
2	20853	20.00% (19.76, 20.25)
3	20902	20.05% (19.81, 20.29)
4	20173	19.35% (19.11, 19.59)
5	18860	18.09% (17.86, 18.33)
Missing	1706	
Rurality		
Urban	83376	79.97% (79.73, 80.22)
Rural	20064	19.25% (19.01, 19.49)
Missing	815	
Ethnicity		
White	78839	75.62% (75.36, 75.88)
Asian	4658	4.47% (4.34, 4.60)
Black	2025	1.94% (1.86, 2.03)
Mixed	1245	1.19% (1.13, 1.26)
Other	1821	1.75% (1.67, 1.83)
Missing	15667	

The rates of adverse medical and surgical outcomes within 90-days, and ligamentous or meniscal reoperation within 5-years, are summarised in Table 2. Overall, 0.97% underwent any reoperation with 90-days (1013/104255; 95% CI 0.91 to 1.03) and 0.65% developed a serious complication (675/104255; 95% CI 0.60 to 0.70) including a rate of 0.47% reoperations for presumed deep infection (494/104255; 95% CI 0.43 to 0.52). The rate of pulmonary embolism was 0.12% (129/104255; 95% CI 0.10 to 0.15), of neurovascular injury was 0.02% (19/104255; 95% CI 0.01 to 0.03), and of fasciotomy was 0.02% (17/104255; 95% CI 0.01 to 0.03). Within 5-years, 3.22% (1746/54275; 95% CI 3.07 to 3.37) underwent a revision ACL reconstruction in the same knee, 2.86% (1553/54275; 95% CI 2.72 to 3.01) underwent ACL reconstruction to the opposite knee, and 0.63% (340/54275; 95% CI 0.56 to 0.70) underwent subsequent meniscal surgery in the same knee. The longer-term rates of revision ACL reconstruction are summarised in the mortality adjusted Kaplan-Meier chart, Figure 2, estimating revision rates out to 15-years by age group. Younger patients were at greater risk of revision as shown (Figure 2, Table 4).

TABLE 2: Adverse outcomes within 90-days and reoperation rates within 5-years

	n	% (95% CI)
90-day adverse outcomes (n=104 255)		
Any re-operation‡	1013	0.97% (0.91, 1.03)
Serious complication †	675	0.65% (0.60, 0.70)
Infection*	494	0.47% (0.43, 0.52)
Lower respiratory tract infection	102	0.10% (0.08, 0.12)
Urinary tract infection	44	0.04% (0.03, 0.06)
Pulmonary embolism	129	0.12% (0.10, 0.15)
Myocardial infarction	4	< 0.01% (0.00, 0.01)
Mortality	14	0.01% (0.01, 0.02)
Stroke	2	< 0.01% (0.00, 0.01)
Acute kidney injury	13	0.01% (0.01, 0.02)
Neurovascular injury	19	0.02% (0.01, 0.03)
Fasciotomy	17	0.02% (0.01, 0.03)
Fatal pulmonary embolus	0	0.00% (0.00, 0.00)

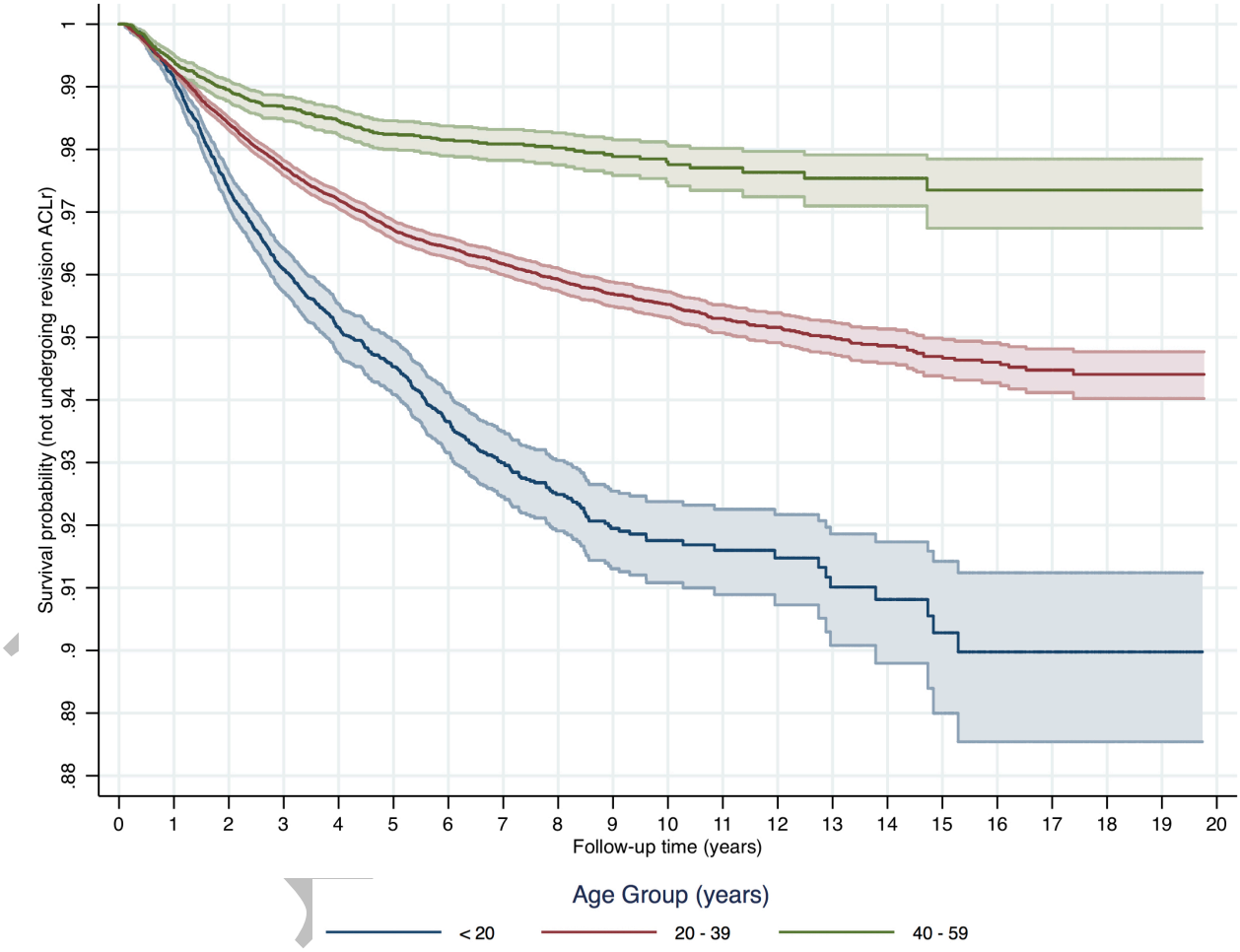
5-year reoperation (n = 54 275)		
Revision ACLr	1746	3.22% (3.07, 3.37)
Subsequent contralateral ACLr	1553	2.86% (2.72, 3.01)
Meniscal surgery	340	0.63% (0.56, 0.70)

236

237 *† = At least one serious complication within 90 days, defined as either pulmonary embolism, myocardial infarction, stroke, infection*
238 *requiring surgery, fasciotomy, neurovascular injury, or death; * = Infection requiring surgery (open or arthroscopic lavage and*
239 *irrigation or debridement of wound or joint); ‡ = Any procedure performed in the same knee (e.g. washout, meniscal repair, repeat*
240 *meniscectomy, chondroplasty, ligamentous surgery, fasciotomy); ACLr = ACL reconstruction*

241

242 **Figure 2: Long-term survival curve (not undergoing subsequent revision ACL reconstruction)**



243

244 ** Age groups < 20 years and > 59 years suppressed due to small numbers*

245

246 Patient factors associated with adverse outcomes within 90-days are summarised in Table 3. Female
247 patients were at lower odds of serious complications and infection; the overall odds of serious
248 complications and of infection fell slightly over time (Table 3). Older age groups (under 20-years vs.

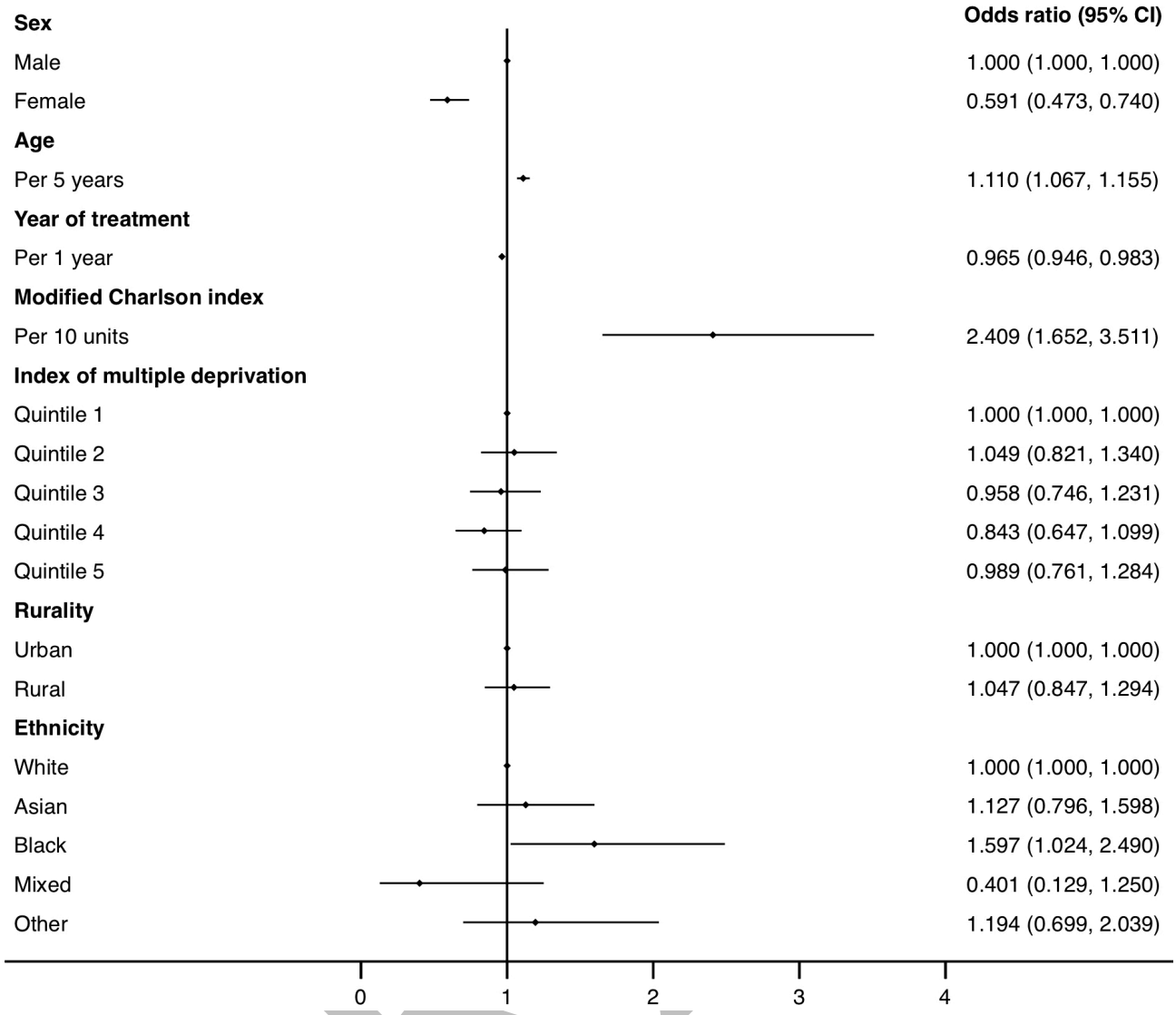
249 20-39-years vs. 40-59-years) were at greater risk of serious complications and pulmonary embolism
250 as were patients with a greater modified Charlson comorbidity index (Table 3). Index of multiple
251 deprivation and rurality did not affect the odds of complications. Patients of black ethnicity were
252 found to be at greater odds of serious complications (adjusted OR 1.61; 95% CI 1.03 to 2.52) mainly
253 due to greater odds of infection in comparison to patients in White ethnicity groups (adjusted OR
254 1.88; 95% CI 1.16 to 3.05). The adjusted odds of serious complications by each patient factor
255 (including patient age) is shown graphically in the forest plot, Figure 3.
256
257 **TABLE 3: Unadjusted and adjusted odds‡ of serious complication, pulmonary embolism, infection**
258

	Serious complication † (90 days)		**Pulmonary embolism (90 days)**		**Infection* (90 days)**	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex						
Male	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.63 (0.51, 0.77)	0.61 (0.49, 0.77)	0.96 (0.63, 1.45)	0.91 (0.58, 1.41)	0.49 (0.38, 0.64)	0.48 (0.36, 0.65)
Age group						
<20	0.61 (0.47, 0.79)	0.60 (0.45, 0.80)	0.35 (0.15, 0.81)	0.42 (0.18, 0.98)	0.65 (0.48, 0.87)	0.64 (0.47, 0.88)
20-39	1.00	1.00	1.00	1.00	1.00	1.00
40-59	1.20 (0.98, 1.46)	1.26 (1.02, 1.56)	2.25 (1.54, 3.30)	2.50 (1.66, 3.76)	0.88 (0.68, 1.13)	0.90 (0.68, 1.18)
60-79	2.25 (1.06, 4.77)	1.94 (0.84, 4.45)	5.74 (1.81, 18.24)	5.32 (1.58, 17.93)	0.82 (0.20, 3.32)	0.45 (0.06, 3.22)
80+	6.83 (0.92, 50.79)	7.63 (1.01, 57.56)	-	-	-	-
Year						
Per year	0.98 (0.96, 0.99)	0.96 (0.95, 0.98)	0.97 (0.94, 1.01)	0.97 (0.93, 1.01)	0.98 (0.96, 1.00)	0.97 (0.94, 0.99)
Modified Charlson comorbidity index						
Per unit	1.11 (1.07, 1.14)	1.10 (1.05, 1.14)	1.16 (1.10, 1.23)	1.11 (1.04, 1.19)	1.07 (1.02, 1.12)	1.08 (1.03, 1.14)
Index of multiple deprivation (quintile)						
1 = least	1.00	1.00	1.00	1.00	1.00	1.00
2	1.08 (0.86, 1.36)	1.05 (0.82, 1.34)	0.73 (0.43, 1.24)	0.62 (0.35, 1.09)	1.16 (0.88, 1.52)	1.18 (0.89, 1.58)
3	0.95 (0.75, 1.21)	0.95 (0.74, 1.22)	0.79 (0.47, 1.33)	0.66 (0.37, 1.15)	0.99 (0.74, 1.31)	1.02 (0.76, 1.37)
4	0.93 (0.73, 1.18)	0.83 (0.64, 1.09)	0.56 (0.31, 1.00)	0.48 (0.25, 0.90)	1.02 (0.77, 1.36)	0.91 (0.67, 1.24)
5 = most	1.02 (0.80, 1.29)	0.98 (0.75, 1.27)	1.05 (0.64, 1.72)	1.06 (0.62, 1.78)	1.05 (0.79, 1.40)	0.97 (0.71, 1.32)
Rurality						
Urban	1.00	1.00	1.00	1.00	1.00	1.00
Rural	1.08 (0.89, 1.30)	1.06 (0.86, 1.31)	0.90 (0.57, 1.42)	0.90 (0.54, 1.49)	1.08 (0.86, 1.34)	1.06 (0.83, 1.36)
Ethnicity						
White	1.00	1.00	1.00	1.00	1.00	1.00
Asian	1.11 (0.79, 1.56)	1.13 (0.80, 1.60)	1.15 (0.53, 2.48)	1.18 (0.54, 2.56)	1.13 (0.76, 1.69)	1.13 (0.75, 1.69)
Black	1.53 (0.99, 2.38)	1.61 (1.03, 2.52)	0.76 (0.19, 3.06)	0.75 (0.18, 3.09)	1.81 (1.13, 2.91)	1.88 (1.16, 3.05)

Mixed	0.35 (0.11, 1.10)	0.40 (0.13, 1.23)	-	-	0.49 (0.16, 1.52)	0.53 (0.17, 1.65)
Other	1.13 (0.67, 1.93)	1.19 (0.70, 2.03)	1.26 (0.40, 3.98)	1.31 (0.41, 4.15)	1.23 (0.67, 2.24)	1.27 (0.69, 2.32)

*‡ = procedure level multi-variable logistic regression model including sex, age group, year, Charlson co-morbidity index, index of multiple deprivation, rurality, and ethnicity; OR = odds ratio; CI = confidence interval; † = At least one serious complication within 90 days, defined as either pulmonary embolism, myocardial infarction, stroke, infection requiring surgery, fasciotomy, neurovascular injury, or death; * = open or arthroscopic irrigation and lavage or debridement; - = suppressed.*

Figure 3: Forest plot of adjusted‡ odds of any serious complication within 90-days



‡ = procedure level multi-variable logistic regression model including sex, age group, year, modified Charlson comorbidity index, index of multiple deprivation (quintile), rurality, and ethnicity

The patient factors associated with the risk of revision ACL reconstruction, contralateral ACL reconstruction, and same side meniscal surgery is summarised in Table 4. Female patients were at lower risk of revision ACL reconstruction (adjusted hazard ratio [HR] 0.81; 95% CI 0.74 to 0.89) and subsequent meniscal surgery (adjusted HR 0.61; 95% CI 0.49 to 0.75), but not contralateral ACL reconstruction (adjusted HR 1.06; 95% CI 0.95 to 1.18; Table 4). Older age groups (under 20-years vs. 20-39-years vs. 40-59-years vs 60-79-years), patients from rural regions or greater deprivation, and patients of Asian and Black ethnicity were less likely to undergo revision ACL reconstruction (Table 4). Patients of Asian ethnicity were also of lower risk of meniscus surgery but increased risk

of contralateral ACL reconstruction (Table 4). All three outcomes were slightly more common over the duration of the study by year of treatment. Patients with a greater modified Charlson comorbidity index were slightly more likely to undergo revision ACL reconstruction (adjusted HR 1.03 per unit; 95% CI 1.01 to 1.06) but not meniscal surgery (adjusted HR 0.99; 95% CI 0.93 to 1.05) or contralateral reconstruction (adjusted HR 0.99; 95% CI 0.96 to 1.03; Table 4).

The rate of mortality was lower in the ACL reconstruction cohort than reported in the general population (risk ratio [RR] 0.09; 95% CI 0.05 to 0.14) (Table 5). For male patients (under the age of 80 years) undergoing ACL reconstruction, the risk of myocardial infarction was lower than in the general population (RR 0.09; 95% CI 0.03 to 0.23). No myocardial infarction was identified for this age-group in a female patient after ACL reconstruction. The rate of stroke (under the age of 75 years) was also lower in the ACL reconstruction cohort than the general population (RR 0.06; 95% CI 0.01 to 0.23). In comparison, the risk of pulmonary embolism (RR 20.60; 95% CI 15.68 to 27.06) and infection (RR 385.91; 95% CI 282.60 to 526.98) was elevated in comparison to general population data. These data correspond to an estimated number needed to harm of 850 (95% CI 720-1039) for one pulmonary embolism and 213 (95% CI 195-233) for one knee joint infection.

TABLE 4: Unadjusted and adjusted hazard ratios for subsequent ipsilateral revision reconstruction, contralateral ligament reconstruction, ipsilateral meniscal surgery

	Revision ACLr		**Subsequent Contralateral ACLr**		**Subsequent meniscal surgery**	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Sex						
Male	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.79 (0.73, 0.87)	0.81 (0.74, 0.89)	1.05 (0.95, 1.15)	1.06 (0.95, 1.18)	0.62 (0.50, 0.76)	0.61 (0.49, 0.75)
Age group						
<20	1.78 (1.64, 1.93)	1.75 (1.61, 1.91)	2.28 (2.08, 2.51)	2.12 (1.92, 2.35)	2.22 (1.88, 2.61)	2.11 (1.78, 2.50)
20-39	1.00	1.00	1.00	1.00	1.00	1.00
40-59	0.52 (0.46, 0.59)	0.51 (0.44, 0.58)	0.44 (0.37, 0.52)	0.42 (0.35, 0.51)	0.36 (0.26, 0.50)	0.34 (0.24, 0.48)
60-79	0.23 (0.07, 0.70)	0.15 (0.04, 0.61)	0.23 (0.06, 0.93)	0.13 (0.02, 0.89)	-	-

80+	-	-	-	-	-	-
Year						
Per year	1.03 (1.02, 1.04)	1.01 (1.00, 1.02)	1.07 (1.06, 1.09)	1.06 (1.04, 1.07)	1.14 (1.11, 1.17)	1.12 (1.09, 1.15)
Modified Charlson comorbidity index						
Per unit	1.03 (1.01, 1.05)	1.03 (1.01, 1.06)	1.00 (0.97, 1.04)	0.99 (0.96, 1.03)	1.01 (0.95, 1.07)	0.99 (0.93, 1.05)
Index of multiple deprivation (quintile)						
1 = least	1.00	1.00	1.00	1.00	1.00	1.00
2	0.87 (0.78, 0.96)	0.88 (0.79, 0.97)	0.93 (0.82, 1.06)	0.95 (0.82, 1.09)	0.98 (0.79, 1.20)	0.94 (0.75, 1.16)
3	0.79 (0.71, 0.88)	0.80 (0.72, 0.89)	1.01 (0.89, 1.15)	1.00 (0.87, 1.15)	0.82 (0.66, 1.03)	0.83 (0.66, 1.04)
4	0.78 (0.70, 0.87)	0.74 (0.66, 0.82)	0.99 (0.87, 1.13)	0.96 (0.83, 1.11)	0.79 (0.63, 0.99)	0.75 (0.60, 0.95)
5 = most	0.68 (0.61, 0.77)	0.64 (0.56, 0.72)	1.03 (0.91, 1.18)	0.96 (0.83, 1.11)	0.58 (0.45, 0.74)	0.52 (0.40, 0.69)
Rurality						
Urban	1.00	1.00	1.00	1.00	1.00	1.00
Rural	0.83 (0.75, 0.91)	0.76 (0.69, 0.84)	1.02 (0.92, 1.13)	0.98 (0.87, 1.11)	0.98 (0.81, 1.17)	0.89 (0.73, 1.08)
Ethnicity						
White	1.00	1.00	1.00	1.00	1.00	1.00
Asian	0.75 (0.62, 0.90)	0.73 (0.61, 0.89)	1.34 (1.11, 1.61)	1.31 (1.09, 1.59)	0.59 (0.37, 0.91)	0.58 (0.37, 0.91)
Black	0.72 (0.55, 0.95)	0.74 (0.56, 0.97)	1.05 (0.78, 1.42)	1.00 (0.74, 1.35)	0.69 (0.38, 1.25)	0.73 (0.40, 1.34)
Mixed	1.15 (0.85, 1.55)	1.09 (0.81, 1.46)	1.26 (0.87, 1.84)	1.09 (0.75, 1.59)	1.17 (0.63, 2.19)	1.05 (0.56, 1.97)
Other	0.48 (0.33, 0.69)	0.50 (0.34, 0.72)	1.04 (0.75, 1.45)	1.07 (0.77, 1.48)	0.46 (0.21, 1.03)	0.49 (0.22, 1.09)

‡ = procedure level Cox proportional hazards model including sex, age group, year, Charlson co-morbidity index, index of multiple deprivation, rurality, and ethnicity. HR = hazard ratio; CI = confidence interval; ACLr = anterior cruciate ligament reconstruction; - = suppressed.

TABLE 5: 90-day adverse event rates in study cohort versus age and/or sex matched general population data

	General population risk % (95% CI) [publication reference]	**Study cohort risk %** (95% CI)	**Risk ratio** (95% CI)
Mortality			
Overall:	0.158% (0.157, 0.159) [10] *	0.013% (0.007, 0.023)	0.09 (0.05, 0.14)
Age < 20 years:	0.007% (0.007, 0.008) [10] *	0.007% (0.000, 0.036)	0.89 (0.12, 6.30)
Age 20 - 39 years:	0.011% (0.011, 0.012) [10] *	0.010% (0.004, 0.020)	0.84 (0.40, 1.77)
Age 40 - 59 years:	0.043% (0.042, 0.044) [10] *	0.031% (0.010, 0.073)	0.73 (0.30, 1.75)
Age 60 - 79 years:	0.233% (0.230, 0.236) [10] *	0.000% (0.000, 0.774)	-
Age 80 + years:	2.043% (2.026, 2.060) [10] *	4.348% (0.110, 21.949)	2.08 (0.31, 14.18)
Myocardial infarction			
Men (age < 80):	0.058% (0.049, 0.067) [38]	0.005% (0.001, 0.013)	0.09 (0.03, 0.23)
Women (age < 80):	0.028% (0.022, 0.035) [38]	0.000% (0.000, 0.016)	-
Pulmonary embolism			
Overall:	0.006% (0.005, 0.007) [36]	0.124% (0.103, 0.147)	20.60 (15.68, 27.06)
Stroke			
Age < 75 years:	0.034% (0.030, 0.039) [12]	0.002% (0.000, 0.007)	0.06 (0.01, 0.23)
Septic arthritis (native knee joint infection)			
Overall:	0.001% (0.001, 0.002) [17] ‡	0.474% (0.433, 0.517)	385.91 (282.60, 526.98)

- = suppressed;

** = Office for National Statistics population level data for England (2016, excluding death due to cancer);*

‡ = excluding iatrogenic causes.

DISCUSSION

Principal findings

Our study of 104 255 procedures shows that serious adverse events occur rarely following ACL reconstruction and that the risk of serious complications has fallen slightly over time. Most medical adverse events occur less frequently following ACL reconstruction than in the general population which is likely a healthy-cohort observation, however there is an important attributable risk of a pulmonary embolism and infection. For every 850 ACL reconstructions performed, one pulmonary embolism and four knee infections could occur and be attributed to the procedure. Around 3.2% of patients undergo revision ACL reconstruction and 2.9% contralateral ACL reconstruction within five-years. These findings will be crucial to informing patients and clinicians when deciding whether to proceed with elective ACL reconstruction. The recognised benefits of the procedure can now be interpreted in the context of the associated potential risks.

Comparison with previous studies

Despite the number of ACL reconstruction procedures performed worldwide,[2,5,26] the adverse outcomes attributable to undergoing the procedure have previously been poorly defined. Several studies have reported adverse events following "knee arthroscopy" but few have reported data specifically for ACL reconstruction in comparison to more commonly performed purely arthroscopic, procedures such as arthroscopic partial meniscectomy.[4,13,21,22,24,32–34,37] In comparison, anterior cruciate ligament reconstruction is a more major intervention, associated with greater operative time and usually both open and arthroscopic incisions and techniques.[31]

In our study, only pulmonary embolism and infection were found to occur at a greater rate than observed in comparative general population data. These findings are similar to those reported recently for a cohort of 699 965 arthroscopic partial meniscectomy procedures.[1] In this meniscectomy cohort, serious complications occurred in 0.32% (95% CI 0.30 to 0.33) in comparison

to 0.65% (95% CI 0.60 to 0.70) following ACL reconstruction using the same definitions. This difference in the serious complication rate was driven in part by a higher reoperation rate for infection following ACL reconstruction at 0.47% (95% CI 0.43 to 0.52) in comparison to 0.14% (95% CI 0.13 to 0.14) following arthroscopic partial meniscectomy.[1] The infection rate identified in our study was similar but statistically more precise with an estimated deep infection rate of 0.43% (58/13401; 95% CI 0.32 to 0.56) ACL reconstruction cases reported in a systematic review of level 2 studies in 2017.[4] It is, however, higher than a rate of 0.14% (7/4933; 95% CI 0.05 to 0.29) reported in a study of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database.[9] With comparison to general population data, the estimated number needed to harm for infection was 213 for our ACL reconstruction cohort versus 749 for the arthroscopic partial meniscectomy cohort.[1]

The rate of pulmonary embolism within 90-days was greater in our ACL reconstruction cohort at 0.12% (95% CI 0.10 to 0.15) in comparison to 0.08% (95% CI 0.07 to 0.09) in the recent arthroscopic partial meniscectomy cohort.[1] No cases of fatal pulmonary embolism were identified following ACL reconstruction. The pulmonary embolism rate was comparable but statistically much more precise than the estimated rate of pulmonary embolism reported in a systematic review of forty-seven ACL reconstruction studies published in 2016, which reported a mean pulmonary embolism rate of 0.14% but with wide confidence intervals (1/704; 95% CI 0.00 to 0.79).[22] The rate is also the same as another 2016 study of 4933 patients reporting a PE rate of 0.12% within 30-days (6/4933).[9] With comparison to general population data, the number needed to harm for pulmonary embolism was estimated to be 850 for ACL reconstruction in comparison to 1390 for arthroscopic partial meniscectomy.[1]

Prescribing data is unavailable in this database and therefore the type and duration of any antibiotic or venous thromboembolic (VTE) prophylaxis given to the patients in this study is unknown and it is likely that local practice varied. Previous work suggested that while antibiotic prophylaxis is routine

366 in most countries, VTE prophylaxis rates vary from around 17% Norway, 51% in the United States,
367 to 79% in Denmark.[18,23] The findings in this study may support further investigation and
368 consideration of routine VTE prophylaxis in this population.
369
370 Other direct surgical complications such as neurovascular injury and fasciotomy could not be
371 compared to general population data. Both neurovascular injury and fasciotomy procedures were
372 identified rarely following ACL reconstruction, at 0.02% in both cases. It must be noted, however,
373 that these rates are approximately 5-10 times greater than reported following arthroscopic partial
374 meniscectomy.[1] The greater risk of these complications, infection, and pulmonary embolism,
375 associated with ACL reconstruction in comparison to arthroscopic partial meniscectomy is
376 unsurprising given the more invasive nature of ACL reconstruction, with additional surgical
377 incisions and more prolonged operative time.[31]
378
379 Regarding reoperation rates, the largest previous study published in 2016 reported an ACL revision
380 rate of 3.6% (587/16336; 95% CI 3.31 to 3.89), utilising US military health record data.[32] Our study
381 reports a very similar rate of revision at 3.22% and adds importantly to these data, reporting
382 contralateral ACL reconstruction in 2.86% and same side meniscal surgery in 0.63% within five-
383 years. The risk of revision ACL reconstruction was considerably greater in younger age groups,
384 although it unknown if this reflects differences in injury rates or differences in propensity to re-
385 operate following injury.
386
387 It is interesting that the risk of revision ACL reconstruction in the same knee was similar to the risk
388 of contralateral ACL reconstruction, which suggests that both the reconstructed ligament and the
389 native opposite knee ligament are at comparable risk of rupture following an ACL reconstruction. A
390 systematic review of nine studies and a smaller number of patients previously reported an ipsilateral
391 graft re-rupture rate of 7.9% (211/2682) but a higher 12.5% (335/2682) risk of contralateral ACL
392 injury.[24] Rates of subsequent meniscal surgery after ACL injury have rarely been reported. Frobell

et. al. reported a 9.7% (6/62; 95% CI 3.6 to 19.9) following ACL reconstruction and up to 49.2% (29/59; 95% CI 35.9 to 62.5) following a non-operative treatment strategy. A much lower rate of subsequent meniscal surgery was observed in our population at 0.63% (95% CI 0.56 to 0.70) which may reflect higher thresholds for subsequent intervention or lower symptomatic injury rates.

Our study found revision reconstruction rates to be lower in women. This finding is similar to a recent systematic review of smaller studies which reported lower rates of ipsilateral graft rupture in women.[27] This review also found women had a higher rate of contralateral knee injury however in our study we found no difference in contralateral knee reconstruction rates in women versus men. Subsequent meniscal surgery rates were also lower in women than men. Our study provides clear reference data for reconstruction rates in men and women and further investigation into the physiological, anatomical, and biomechanical factors that underlie these differences is warranted, with specific focus on preventative interventions. These findings will be crucial to the education of patients following ACL injury and reconstruction and inform collaboration between patients, physiotherapists, and clinicians in optimising current and future rehabilitation strategies.

Strengths and limitations

Our study is strengthened by the inclusion of 104 255 ACL reconstruction cases over a twenty-year period, utilising data from the complete national health database for England, UK. To our knowledge, this is by far the largest reported series of ACL reconstruction cases and the largest to report adverse outcomes. Patients undergoing bilateral surgery (within 6 months), multiple ligament reconstruction, ACL repair, synthetic graft procedures, or articular cartilage surgery were excluded. Patients undergoing concurrent meniscal procedures were, however, included as these procedures were common (approximately 28%) and therefore including these cases makes the cohort more representative of normal practice. Our study is also the most comprehensive evaluation of adverse outcomes, including the broad range of surgical and medical complications that may occur and, where possible, risk has been compared to age-sex matched general population data. The comparison

to general population data is relative crude but together with adverse outcome data following arthroscopic partial meniscectomy extracted from the same database, provides for the first time an important estimate of the attributable risk associated with ACL reconstruction.

HES data includes diagnosis and intervention data from admitted hospital care episodes in the national health service, England, and is collected routinely for hospital reimbursement, audit and research purposes. Although HES comprehensively records diagnosis and procedural data for patients admitted to hospital, there are some limitations. Although our data included a patient-specific modified Charlson comorbidity index, there are some important patient specific factors such as body mass index and smoking status that are not recorded in HES and are likely to impact upon risk. Regarding the accuracy of data coding in the database, the Charlson comorbidity index as calculated from HES diagnosis fields and records of serious vascular complications have been validated against primary care data.[8,40] Some patient variables such as ethnicity, however, may be less reliably coded. It is also important to note that the OPCS-4 codes used to identify ACL reconstruction procedures for our patient cohort will have captured some posterior cruciate ligament reconstruction procedures. This is inevitable given the nature of the codes used for this procedure but the proportion of the posterior cruciate ligament reconstruction procedures performed is very small in comparison to ACL reconstruction and therefore we believe these procedures are unlikely to have materially altered our findings.[3] The first ACL reconstruction per patient, per knee, was considered the primary procedure and revision procedures identified as any subsequent ACL reconstruction. Any primary procedure undertaken prior to 1st April 1997, however, would be not be identified and therefore it is possible a small number of revision procedures could have been included in our cohort as no "revision" code is available. From HES data we are also unable to determine the impact from operative factors, such as reconstruction technique and choice of graft on outcome as these operative techniques are not recorded.

Diagnoses from primary care or the outpatient department are not available in the HES inpatient dataset unless these diagnoses were associated with a later hospital admission for care or surgery. This means, for example, that the reported revision ACL reconstruction and contralateral ACL reconstruction rates in our study will be lower than the true ACL injury rates in the population. Similarly, soft tissue infections managed non-operatively will not have been recorded. Another limitation of the HES database is that laboratory and radiological data is not recorded. Therefore, whilst cases of knee open or arthroscopic irrigation and lavage or debridement with an associated 'haemarthrosis' diagnosis code were not recorded as infections, from the remaining lavage and debridement procedures we cannot distinguish procedures performed for a laboratory confirmed infection from those with a suspected infection. The clinical implications in each case may be quite different and an important limitation of this observational HES data. It must also be considered that some patients may have undergone their primary ACL reconstruction in the national health service but subsequent care in the private health sector. This is unlikely to have affected the record of adverse events within 90-days, as patients are highly likely to have returned to a national health hospital in these cases. In the longer term, however, some patients may have chosen to have revision ACL reconstruction or contralateral ACL reconstruction in the private health sector and would not be captured and this must be considered when interpreting our long-term reoperation data. Minor adverse outcomes that may have been managed in primary care would also not be captured. Our findings are, however, by far the most comprehensive to date regarding the true risk of serious complications associated with undergoing ACL reconstruction and, we believe, should be broadly generalisable to ACL reconstruction practice in developed countries, worldwide.

Conclusion

Whilst the risk of adverse events following ACL reconstruction is greater than following arthroscopic partial meniscectomy, the overall risk is still low and most medical complications (myocardial infarction, stroke, death) occur less frequently following ACL reconstruction than in the general population. Nevertheless, rare but serious complications including pulmonary embolism,

infection, fasciotomy and neurovascular injury may by provoked by undergoing ACL reconstruction. Same side and contralateral knee ACL reconstruction was performed in 3.2% and 2.9% of cases within 5-years of primary ACL reconstruction respectively. Our findings will be crucial to informing patients considering the relative risks and benefits of undergoing early ACL reconstruction in comparison to the emerging treatment strategy of rehabilitation and optional delayed ACL reconstruction. Further work is required to optimise not only the primary treatment selection but also strategies to reduce reinjury rates.

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